Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned **"VERSION WITH MARKINGS TO SHOW CHANGES MADE"**. Subject matter that was deleted is in brackets and subject matter that was added is underlined. Support for these amendments is in the dependent claims and in the specification as filed. No new matter is added to this application with the above amendments. All of the claims will be renumbered and their dependency changed, as appropriate, once the claims are in condition for allowance.

The Examiner acknowledged receipt of the Information Disclosure Statement, filed in the present application, and enclosed a copy of Form PTO-FB-A820, as initialed by the Examiner. The Examiner did not acknowledge the claim for domestic priority under 35 USC 119(e); however, such a claim was made in the Preliminary Amendment, which was submitted with the filing of the present application. Attached hereto is another copy of this amendment, for the Examiner's reference.

With the present response, Applicants have included a Supplemental Information Disclosure Statement and a copy of the references cited therein, for the Examiner's consideration. Also, for the Examiner's information, a formulation within the scope of the present application was submitted to and approved by the FDA for marketing in the U.S.

Finally, Applicants would appreciate it if the Examiner would send them another copy of the Filing Receipt for the present application. A copy of this Filing Receipt has been requested in a telephone call to the USPTO Customer Service Center, but has not yet been received.

RESTRICTION REQUIREMENT

The Examiner has required restriction to one of the following inventions under 35 USC 121: Group I. (Claims 1-11) drawn to a composition and sertraline compound; and Group II. (Claims 12-19) drawn to a method of using liquid concentrate of sertraline or method of treating diseases. According to the Examiner, the inventions are distinct, each from the other because Inventions group I and group II are related as a compound and its composition and process of using the product. The Examiner admitted that the use as claimed cannot be practiced with a materially different product; however, the Examiner concluded that since the product is not

allowable, restriction is proper between said compound and its composition and method of using, referring to MPEP §806.05(I).

Applicants do not believe that MPEP §806.05(I), cited by the Examiner, is determinative of the restriction requirement for the claims of the present application. This section deals with applications containing claims to all three categories -- a product, a process for making the product and a process of using the product. This section states that if the product claims are not allowable, restriction is proper between the process of making and the process of using; and the applicant may be required to elect either (1) the product and process of making it, or (2) the process of using.

The present application does not contain the above three categories of claims. The present application contains claims to a sertraline compound and composition and a method of using that composition. In fact, the Examiner has described the claims of the present application as a compound and its composition and a process of using the product.

Thus, the more relevant section is MPEP § 806.05(h), which deals with applications containing claims to a product and a process of using the product. According to this section, the product must be joined with the process of using the product, unless the examiner can make a showing of distinctness between the process of using and the product. In fact, this section of the MPEP is also referenced in MPEP §806.05(I), cited by the Examiner, which states that the product must also be joined with the process of using in grouping (2) described above, unless the examiner can make a showing of distinctness between the process of using and the product.

As noted above, the Examiner has already admitted that, for the present application, the use as claimed cannot be practiced with a materially different product. Therefore, according to the MPEP, especially MPEP § 806.05(h), Applicants believe that the claims of the present application should be joined for examination purposes; especially claims 1-10 (which are now claims 1 and 7-10 as amended) should be joined with claims 12-19 (which are now claims 12 and 14-19, as amended). Applicants believe that this is particularly true since claims 12-19 (now claims 12 and 14-19, as amended) have been amended to be dependent on claim 1, as amended.

During a telephone conversation with Martha A. Gammill on 2/5/2001, a provisional election was made with traverse to prosecute the invention of group I, claims 1-11. According to the Examiner, affirmation of this election must be made by applicant in replying to this Office action. Claims 12-19 have been withdrawn from further consideration by the examiner (37 CFR 1.142(b)) as being drawn to a non-elected invention.

Applicants hereby affirm the election of Group I (claims 1-11). However, Applicants would continue to traverse this restriction requirement and would request that the Examiner reconsider it, for the reasons given above.

CLAIM REJECTIONS – 35 USC § 102

Claims 1-3 have been rejected under 35 USC 102(b) as being anticipated clearly by Howard et al (U.S. 5,597,826). The Examiner states that Howard et al. discloses a pharmaceutical composition containing sertraline hydrochloride (see col. 20, line 31) with a dose from 0.1 mg to 200 mg (see col. 24, lines 7-8), suspending agents, non-aqueous vehicles, and preservatives (see col. 22, lines 51-56). According to the Examiner, this is identical to the claims.

The Howard reference is directed to combination pharmaceutical therapy and discloses combination pharmaceutical compositions containing sertraline, or a pharmaceutically acceptable salt thereof, and a compound of formula I, which is an agonist or antagonist of the serotonin 1 ($5\text{-}HT_1$) receptor. The dose, which the Examiner refers to at col. 24, lines 7-8, of the Howard reference, is for doses of the compound of formula I, and not for sertraline or its salts. Furthermore, the suspending agents, non-aqueous vehicles and preservatives, referred to by the Examiner, are to be included in conventional liquid preparations for the oral administration of the combination of the active ingredients, as described above, and not for the administration of sertraline or its salts alone.

Thus, for the reasons given above, the pharmaceutical compositions disclosed in Howard are not identical to claims 1-3 of the present application, which are directed to pharmaceutical compositions containing one active ingredient. Therefore, Applicants respectfully request that the rejection of claims 1-3 under 35 USC § 102(b) be withdrawn.

CLAIM REJECTIONS – 35 USC §103

Claims 4-11 have been rejected under 35 USC 103(a) as being unpatentable over Howard et al (U.S. 5,597,826). The Examiner states that Howard et al. discloses a pharmaceutical composition containing sertraline hydrochloride (see col. 20, line 31) with a dose from 0.1 mg to 200 mg (see col. 24, lines 7-8), suspending agents, non-aqueous vehicles such as ethyl alcohol, and preservatives (see col. 22, lines 51-56); in addition, oral pharmaceutical formulations can be flavored by means of various agents (see col. 23, lines 56-58). Also, the Examiner states that the reference indicates that pharmacologically acceptable anions include methanesulfonate (see col. 20, lines 60-61).

As discussed above, the Howard reference is directed to combination pharmaceutical compositions containing a combination of two active ingredients, and the pharmaceutical formulations described therein are to such combinations, and not to the administration of sertraline or its salts alone. As noted above, the dose referred to by the Examiner is for doses of the compound of formula I, and not for sertraline or its salts. Also, as noted above, the suspending agents, the non-aqueous vehicles, the preservatives and the flavoring agents are all for use in pharmaceutical formulations, containing a combination of two active ingredients, and not for formulations of sertraline or its salts alone. Furthermore, the reference at col. 20, lines 60-61, of the Howard reference to pharmacologically acceptable anions, including methanesulfonate, is to the preparation of salts of the compound of formula I, and not sertraline, as claim 11 of the present application.

Thus, for the above reasons, Applicants believe that claims 4-11 (which are now claims 1 and 7-11, as amended), which are directed to pharmaceutical compositions containing one active ingredient, are clearly patentable over the Howard reference and respectfully requests the withdrawal of this rejection under 35 USC §103.

In fact, the Examiner admits that Howard et al. differs from the instant invention in that 8 to 20% ethanol is in glycerin, the flavoring agent is menthol, the preservative is butylhydroxytoluene, and each ml of the concentrate contains 151 mg of ethanol, 0.5 mg of menthol, 0.1 mg of butylhydroxytoluene, and 1011 mg of glycerin. However, the Examiner continues and cites the Johnson reference, stating that Johnson (EP 0768083 A2) discloses an oral pharmaceutical composition for

treating myocardial infarction patients; the composition contains sertraline or its pharmaceutically acceptable salt, flavoring agents, and diluents such as ethanol, propylene glycol, and glycerin (see from page 3, lines 58, to page 4, line 24). The Examiner also cites Pollinger et al (U.S. 6,136,347) and states that it discloses pharmaceutical preparations for masking unpleasant substances in liquid form, which can contain a protective substance such as butylhydroxytoluene for an excipient media (see col. 9, lines 37-38). The Examiner also notes that Pollinger et al. discloses liquid auxiliaries such as ethanol, propylene glycol, polyethylene glycol (see col. 8, lines 58-60) which can be employed in an amount of from 5 to 40% (see col. 6, lines 54-56).

In reply, Applicants would point out that no where does the Johnson reference disclose or suggest Applicants' nonconventional pharmaceutical form of sertraline hydrochloride as an oral concentrate, having Applicants' unique combination of excipients of ethanol and glycerin. The Johnson reference has simply listed diluents commonly used in pharmaceutical formulations. Such a listing may make it "obvious to try" these different diluents, but this is not the proper standard for obviousness under 35 USC §103 (see, e.g., In re O'Farrell, 7 USPQ2d 1673, 1680 (Fed. Cir. 1988)). The Examiner even admits that the Johnson reference is silent as to the claimed range of ethanol in glycerin, as claimed in the present claims, as amended.

Furthermore, Applicants do not believe that the Pollinger reference makes up for the deficiencies in the disclosure of the Johnson reference. In fact, the Pollinger reference, in Applicants' opinion, is from a non-analogous art area. In Pollinger, the flavor-masking of the pharmaceutical compositions for oral administration is achieved by microencapsulation of the active ingredient (see col. 1, line 66, to col. 2, line 2). Also, Pollinger states that the microcapsules so prepared can be further formulated to give medicaments and describes possible administration forms for the microcapsules, for example, oily juice formulations or sachets (see col. 8, lines 42-44). Thus, to the extent that BHT is present in the Pollinger formulations, it is used as an antioxidant to protect the oily excipient media in the oily juice formulations of the microcapsules (see col. 9, lines 33-38). Furthermore, the liquid auxiliaries mentioned in Pollinger are to be combined with the oily carriers in the oily juice formulations of the microcapsules (see col. 8, lines 58-62). And finally, the percentage range in Pollinger, referred to by the Examiner, is for antiadhesive

agents, which may be used to decrease or avoid completely the adhesion or the agglutination of particles during the microencapsulation process (see col. 6, lines 46-56).

Thus, for the above reasons, the Pollinger reference, which clearly relates to microencapsulation for masking the taste of offending active ingredients, is not relevant to the present application and should be withdrawn as a reference. Therefore, Applicants do not believe that the Pollinger reference is properly combinable with the other references cited above, under 35 USC §103 and would request the withdrawal of this rejection of the claims of the present application.

The Examiner admits that in reference to the flavoring agent being menthol, the reference is silent; however, the Examiner states that Howard et al does teach that oral pharmaceutical formulations can be flavored by means of various agents (see col. 23, lines 56-58). Therefore, the Examiner concludes that if the skillful artisan in the art had desired to develop a unique menthol taste in the oral pharmaceutical composition containing sertraline hydrochloride, it would have been obvious for the skillful artisan in the art to have selected menthol flavor as the masking agent for the product.

In response, Applicants would again remind the Examiner that the Howard reference describes the preparation of combination pharmaceutical compositions for the administration of the combination of two active ingredients of sertraline, or a pharmaceutically acceptable salt thereof, and a compound of formula I, which is an agonist or antagonist of the serotonin 1 (5-HT_1) receptor. The Howard reference states that such pharmaceuticals can be suitably sweetened and/or flavored by means of various agents of the type commonly employed for such purposes (see col. 23, lines 56-58). However, the use of flavoring agents as proposed by the Examiner, from looking at the Howard reference, simply did not work satisfactorily for the present invention.

As stated in the present specification at page 3, lines 18-23, development of an oral liquid dosage form of sertraline has been complicated by the objectionable bitter taste and astringency sensation imparted by the drug in liquid form. Thus, direct ("ready-to-use") oral liquid solutions or suspensions of sertraline, such as those described in the art, have an objectionable taste, *despite the inclusion of a variety of taste-masking or flavoring agents* (emphasis added). Thus, Applicants

have shown that the use of flavoring agents, as suggested by the Examiner, did not work satisfactorily for the present invention, further demonstrating the non-obviousness of the present invention.

The Examiner also admits that with respect to each ml of the concentrate containing 151 mg of ethanol, 0.5 mg of menthol, 0.1 mg of butylhydroxytoluene and 1011 mg of glycerin, the references are silent. However, according to the Examiner, the pharmaceutical oral composition can contain various excipients with varied concentrations so as to meet special needs for the patients' use. Therefore, the Examiner states that the composition of various known excipients do not have any patentable weight in the instant invention in the absence of unexpected results.

In reply, Applicants would point to the present specification, especially page 6, lines 25-31, where they have shown that, in addition to acceptable taste upon administration, the oral concentrate of the present invention has other surprising and unexpected advantages. It provides convenience in measuring different doses, which are needed for certain indications, as well as good physical/chemical stability characteristics throughout the product's shelf-life and use interval. Also, since the concentrate of the present invention is a solution, it is preferred over a suspension for ease of manufacture and optimal control of dosing homogeneity. Thus, Applicants have shown that their unique combination of excipients in the oral concentrate of the present invention has resulted in surprising and unexpected properties, such as acceptable taste, stability and solubility, not taught or suggested in the prior art. Therefore, Applicants believe that the claims of the present application, as amended, are patentable over the prior art cited by the Examiner.

Finally, the Examiner concludes that if the skillful artisan in the art had desired to develop a unique oral pharmaceutical composition containing sertraline hydrochloride, claimed various excipients with a menthol flavor, it would have been obvious for the skillful artisan in the art to have used Johnson's diluents such as ethanol and glycerin and Pollinger et al.'s butylhydroxytoluene preservative in Howard et al's oral pharmaceutical formulation so as to obtain an idealistic liquid product.

In combining these references and making this rejection, the Examiner has relied on impermissible hindsight reconstruction and has, in effect, used Applicants' own invention against them. In making the above rejection, the Examiner has had to

"pick and choose" different elements from the above references and then pieced them together in order to achieve Applicants' invention. This is the essence of impermissible hindsight reconstruction.

The Federal Circuit has warned against doing this especially "in the case of less technologically complex inventions, where the very ease with which the invention can be understood may prompt one to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher." (quoting from In re Dembiczak, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999)).

Furthermore, the Federal Circuit has stated that the best defense against doing this is to insist on a rigorous application of the requirement for motivation:

"Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement of a showing of the teaching or motivation to combine prior art references. . . . Combining prior art references without evidence of such a suggestion, teaching or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability – the essence of hindsight." (again quoting from In re Dembiczak, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999)).

In the absence of Applicants' own disclosure, Applicants would assert that the Examiner has not supplied the requisite suggestion, teaching or motivation to combine the above cited references in order to achieve the nonconventional oral concentrate of the present invention having the unique combination of excipients. Applicants have clearly distinguished these references from the present invention, including showing that one reference is from a non-analogous art area and not properly combinable with the other references. Furthermore, no where do these references teach or suggest Applicants' unique combination of excipients needed to achieve the desired product having the unexpected and advantageous properties described in the present specification. Thus, Applicants believe that claims 4-11 (now claims 1 and 7-11 as amended) are patentable over the Howard reference, the Johnson reference and the Pollinger reference, either singly or in combination, and request that the rejection of these claims under 35 USC § 103 be withdrawn.

On the basis of the above amendments and remarks, Applicants respectfully request reconsideration of this application, as amended, and the early allowance of all the claims, including claims 1, 7-12 and 14-19, as amended.

Respectfully submitted,

Date: 10 August 2001

Martha A. Gammill
Attorney for Applicant(s)
Reg. No. 31,820

Pfizer Inc.
Patent Department
Eastern Point Road
Groton, CT 06340
(860) 441-5940

Attachments:
Petition for Extension of Time
Claims: Version with Markings to Show Changes Made
Supplemental Information Disclosure Statement
Copy of Preliminary Amendment dated October 11, 1999

ATTACHMENT

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claim 1 has been amended as follows:

1.(Amended) A pharmaceutical composition which comprises:
an essentially nonaqueous, liquid concentrate for oral administration comprising about 15 to about 30 mg/ml [an amount] of sertraline hydrochloride [or a pharmaceutically acceptable salt thereof] and [one or more essentially nonaqueous] pharmaceutically acceptable excipients; [wherein at least one of the excipients is liquid.] wherein the excipients are ethanol and glycerin in an amount of about 8 to about 20% ethanol (by weight) in glycerin.

Claims 2-6 have been cancelled.

Claims 7-11 have been retained.

Claim 12 has been amended as follows:

12. (Amended) A method of using an essentially nonaqueous, liquid concentrate of sertraline hydrochloride [or a pharmaceutically acceptable salt thereof] of claim 1 to prepare an aqueous solution of sertraline which comprises diluting the concentrate in an aqueous diluent prior to oral administration.

Claim 13 has been cancelled.

Claim 14 has been retained.

Claim 15 has been amended as follows:

15. (Amended) A method of treating or preventing diseases or conditions which are caused by disorders of the serotonergic system which comprises:

a) diluting an essentially nonaqueous, liquid concentrate of sertraline hydrochloride [or a pharmaceutically acceptable salt thereof] of claim 1 in an aqueous diluent; and

b) orally administering the resulting aqueous solution to a patient in need thereof.

Claim 16 has been retained.

Claim 17 has been amended as follows:

17. (Amended) A method of treating or preventing diseases or conditions selected from the group consisting of depression, anorexia, chemical dependencies,

anxiety-related disorders, premature ejaculation, cancer and post myocardial infarction, which comprises:

a) diluting an essentially nonaqueous, liquid concentrate of sertraline hydrochloride [or a pharmaceutically acceptable salt thereof] of claim 1 in an aqueous diluent; and

b) orally administering the resulting aqueous solution to a patient in need thereof.

Claims 18 and 19 have been retained.